REMARKS

I. Status of Claims:

Upon entry of the above amendment, claims 1-6, 13-25, 28, 31-38, and 42-45 will be pending in this application, claims 27, 29, 30, 40, and 41 having been newly canceled without prejudice. Claims 1-6 and 13-23 are withdrawn as being drawn to a nonelected invention.

Claims 24, 31, 35, and 44 are amended above. Support for the claim amendments can be found throughout the application as filed, for example, in canceled claims 27, 30, 40, and 41 and in Example 2[1] at pages 26-27 of the specification. Accordingly, no new matter has been added.

II. Information Disclosure Statement:

Applicants thank the Examiner for considering the Information Disclosure Statements (IDSs) filed on February 12, 2008, May 21, 2008, June 11, 2008, August 29, 2008, and September 13, 2008 (*see,* Office Action, page 2, section 6).

Applicants are submitting a new IDS along with this Amendment. Applicants request that the Examiner consider the references submitted in this IDS and return an initialed copy of the Form PTO-1449 with the next Office Communication.

III. Withdrawn Rejections:

Applicants gratefully acknowledge that the Examiner has withdrawn the rejection of claims 24, 25, 27-38, and 40-45 under 35 U.S.C. § 103(a) as being unpatentable over Oka *et al.*, in view of Reff and Heard (*see,* Office Action, page 3, section 7).

IV. Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description:

Claims 24, 25, 27-38, and 40-45 are newly rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Action alleges that there is insufficient written description as to the genus of antibodies that would possess increased cytotoxicity in minibody form (*see,* Office Action, page 3, section 9).

Specifically, the Action alleges that Applicants' 2D7 antibody is not representative of the genus given (i) the data in Genestier *et al.*, which purportedly "support [that] not all HLA class I antibodies have cytotoxic activity and [(ii)] the instant disclosure does not characterize or identify the epitope or structure connected with the cytotoxic activity" (*see,* Office Action, page 5, second full paragraph).

As a preliminary matter, Applicants note that independent claims 24 and 35 have been amended herein.

Amended ***claim 24*** recites: A method for producing an HLA-A antigen-recognizing minibody, the method comprising: (a) identifying a whole antibody that recognizes a domain consisting of α1 and α2 of an HLA-A antigen; (b) producing a minibody version of the antibody of (a); and (c) assaying a cytotoxic activity of the minibody, wherein the minibody is an scFv or a diabody.

Amended ***claim 35*** recites: A method of producing a minibody, the CDRs of which are derived from the CDRs of a whole antibody that recognizes a domain consisting of α1 and α2 of an HLA-A antigen, wherein the minibody has a level of cytotoxic activity greater than that of the whole antibody, the method comprising: (a) providing a DNA encoding the minibody; (b) expressing the minibody from the DNA; and (c) confirming that the expressed minibody possesses cytotoxic activity greater than that of the whole antibody, wherein the minibody is an scFv or a diabody.

Turning first to the Action's reliance on Genestier, Applicants respectfully submit that Genestier actually supports Applicants' compliance with the written description requirement rather than detracting from it. The Action states:

> Genestier et al. teach MoAb90 and YTH862 induce apoptotic cell death of activated T lymphocytes but antibodies B9.12.1, W6/32, and TP25.99 had little or no apoptotic effect (see table 2). Genestier, et al. suggest that α1 domain induced apoptosis does not require cross-linking and excludes a possible Fc-receptor mediated antibody-dependent-cytotoxicity mechanism (see discussion page 3636). Thus, the broad genus of HLA class I antibodies would not be cytotoxic. (*see,* Office Action, page 4, first paragraph).

Applicants note that this rejection hinges in part on the Office's incorrect interpretation of "cytotoxic activity." The Office Action appears to assume that cytotoxic activity means only apoptosis. This is not correct. The term "cytotoxic activity" is used in the claims and the

specification to cover not only a cell death-inducing activity such as apoptosis, but also a cell growth-suppressing activity. Applicants draw the Examiner's attention to dependent claims 34 and 43 of this application, which further limit the "cytotoxic activity" of independent claims 24 and 35, respectively, to be a "cell growth-suppressing activity." Note also the disclosure at page 30, line 20, to page 31, line 3, of the application as filed. This section of the application clearly indicates that cytotoxicity does not necessarily require apoptosis, because the exemplified embodiment, 2D7DB, induces cytotoxicity by a non-apoptotic mechanism. When the application and the pending claims are properly understood, Genestier and the other Examiner-cited art actually support Applicants' compliance with the written description requirement.

Genestier cites 16 references that apparently teach that:

> Engagement of HLA class I molecules on human T cells by either soluble or cross-linked antibodies . . . was reported to either inhibit or induce cellular proliferation, depending on the conditions. In addition, several studies have shown that HLA class I ligation on T cells may result in growth arrest, anergy, and eventually apoptosis induction. (*see,* page 3629, left column, first paragraph, last two sentences).

The cited section evidences that, at the time of the filing of this application, it was known that HLA class I ligation could inhibit cellular proliferation and/or cell death (*i.e.,* have cytotoxic activity). All of the antibodies that Genestier taught inhibited cellular proliferation and/or induced apoptosis. Thus, if the Action were to properly construe "cytotoxicity" to be more than just apoptosis, Genestier supports that the genus of HLA class I antibodies would be cytotoxic. In sum, all of the HLA class I antibodies taught by the cited reference appear to have cytotoxic activity. Thus, Genestier's findings with respect to these antibodies actually support Applicants' compliance with the written description requirement.

The Action's reliance on Carnegie Mellon Univ. v. Hoffman-La Roche Inc., 541 F.3d 1115 (Fed. Cir. 2008) and In re Alonso, No. 2008-1079 (Fed. Cir. 2008) is misplaced. These cases are not relevant to the adequacy of support of the instant claims, as these cases relate to situations involving a lack of predictability and lack of knowledge in the art regarding molecules recited in the claims. The issue in both of those cases was the adequacy of the written description provided by a single species - a single polymerase in Carnegie Mellon and a single antibody that binds an antigen in neurofibrosarcoma in Alonso - *in unpredictable and unchartered areas.* In

Carnegie Mellon, very little was known about any bacterial polymerase other than the polymerase described in the application; in Alonso, the application did not even characterize the antigen to which the monoclonal antibodies were to bind, and in fact left it very open-ended. In striking contrast, the antigen specified in the present claims (as amended) is narrowly defined as being a particular, well-defined region (the α 1 and α 2 domains) of a well-characterized protein, the sequence of which is well known in the art: HLA-A. Thus, the instant case is more akin to Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed.Cir.2004), than to Carnegie Mellon or Alonso. In Noelle, the Federal Circuit held that a claim broadly drawn to a genus of antibodies that bind to a given antigen satisfies the written description requirement so long as the antigen is "well characterized" (for example, where the sequence of the antigen is known). Here, the sequence and structural characteristics of HLA-A proteins and their various domains were of course well known to those of skill in the art at the priority date (*see, e.g.*, the discussion of the HLA domains in the first sentence of Genestier). Thus, there is no question that the antibodies and minibodies recited in the present claims (particularly claim 24 and its dependents) satisfy the written description requirement as elaborated in Noelle.

Claim 35 defines the recited minibody not only in terms of the antigen to which its parental antibody binds, but also by means of a functional limitation: "the minibody has a level of cytotoxic activity greater than that of the whole antibody." Accordingly, the relevant Federal Circuit decisions include not only Noelle (for the reasons elaborated above) but also Invitrogen Corp. v. Clontech Lab. Inc., 429 F.3d 1052, 1071-74 (Fed. Cir. 2005), which concerned the written description requirement in the context of a functional limitation. In Invitrogen, the applicant claimed a compound (a genetically modified reverse transcriptase (RT)) in terms of biological functions (DNA polymerase and RNAse H activity). The specification disclosed the sequence of just one species of genetically modified RT. The Invitrogen court found that provision of the DNA and amino acid sequences of a single representative embodiment of the claimed modified RT enzyme was sufficient to support the broad claim. Similarly, the embodiment disclosed at Examples 2, 3 and 5 of the present specification, coupled with (a) what is known in the art and disclosed in the specification about the HLA-A antigen, about generating

antibodies, and about preparing minibody versions of such antibodies; and (b) what is disclosed in the specification about assaying cytotoxic activity, together constitute more than adequate support for the claimed invention. Federal Circuit case law mandates a finding that Applicants have complied with the written description requirement.

Based on the foregoing, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, written description, be reconsidered and withdrawn.

V. Rejections Under 35 U.S.C. § 102(b):

Claims 24, 25, 27-29, 33, and 34 are rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by Woodle *et al.* (*Transplantation*, 64:140-146, 1997) (*see,* Office Action, pages 6-7, section 11). Applicants note that the rejection of claims 27 and 29 is moot as those claims have been canceled herein.

According to the Examiner, Woodle teaches digestion of 5H7 (an IgG2a anti-HLA monoclonal antibody), with pepsin or papain to produce $F(ab')_2$ or Fab fragments, as well as the measurement of cytotoxic activity for both the full length 5H7 antibody and the $F(ab')_2$ or Fab fragments.

To anticipate a claim, the cited reference must teach *each and every* claim limitation. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

There are two independent claims under examination in this application – *i.e.*, claims 24 and 35. Both of these independent claims have been amended herein to specify that the antibody "recognizes a domain consisting of α1 and α2 of an HLA-A antigen." Woodle teaches F(ab) and $F(ab')_2$ fragments of a murine anti-human monoclonal antibody, 5H7, specific for the **α3** domain of human class I MHC (*see,* page 140, Background and Results; and page 142, right column, second and third paragraphs). Nowhere in Woodle is there any teaching or suggestion of antibody that recognizes a domain consisting of α1 and α2 of an HLA-A antigen. In addition, Woodle does not teach or suggest an scFv or a diabody.

Because Woodle does not teach each and every limitation of Applicants' amended independent claims, Woodle does not anticipate claims 24, 25, 28, 33, and 34. Accordingly,

Applicants respectfully request reconsideration of this rejection under 35 U.S.C. § 102(b) and withdrawal of the same.

VI. Rejections Under 35 U.S.C. § 103(a):

Claims 24, 25, 27-38, and 40-45 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Woodle in view of Ghetie *et al.* (U.S. Pat. No. 6,368,596), as evidenced by the specification (*see,* Office Action, pages 8-10, section 15). Applicants note that the rejection of claims 27, 29, 30, 41, and 42 is moot as those claims have been canceled herein.

To set forth a *prima facie* case of obviousness under 35 U.S.C. § 103(a) three conditions must be met: (i) the Office must provide some explicit reason that would lead one of ordinary skill to modify the primary reference with the teachings of the secondary reference; (ii) the combination of the cited references must actually teach all claimed limitations; and (iii) the ordinary artisan in the relevant field must have some expectation of success on producing the claimed invention. *See, KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984).

As a preliminary matter, Applicants note that both independent claims 24 and 35 have been amended herein to specify that the antibody "recognizes a domain consisting of α1 and α2 of an HLA-A antigen."

As noted in section V above, nowhere in Woodle is there any teaching or suggestion of antibody that recognizes a domain consisting of α1 and α2 of an HLA-A antigen, much less an scFv or a diabody version of such an antibody. Woodle is focused on an antibody that recognizes the α 3 domain of an HLA class I antigen and $F(ab')_2$ or Fab fragments thereof.

Ghetie does not remedy this deficiency, as it also fails to teach antibody that recognizes a domain consisting of α1 and α2 of an HLA-A antigen.

Therefore, even if there was some reason to combine Woodle with Ghetie, the combined teachings would not teach all the limitations of Applicants' claims. Thus, the Office has failed to set forth a *prima facie* case of obviousness.

Accordingly, Applicants respectfully request reconsideration of this rejection under 35 U.S.C. § 103(a) and withdrawal of the same.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance and therefore request that a Notice of Allowance be timely issued.

No fees are believed to be due with this filing; however, if any fees are due, please apply any required charges or credits to Deposit Account 06-1050 referencing 14875-0141US1.

If the prosecution of this application can be advanced by a telephonic interview, the Examiner is encouraged to call the undersigned at the telephone number listed below.

Respectfully submitted,

Date: February 17, 2009

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